NCERQA STAR GRANT ABSTRACT

EPA Grant Number: (please leave blank, I will add later)
Title: Molecular Characterization of a Biological Threshold in Developmental Toxicity
Investigator(s): Thomas B. Knudsen, Ph.D.
Institution: Jefferson Medical College
EPA Project Officer: Chris Saint
Project Period: October 1, 1999 – September 30, 2002
Research Category: Children's Vulnerability to Toxic Substances

Objectives/Hypothesis: The goal of this research is to characterize, in molecular terms, the biological basis of a threshold in developmental toxicity and place this mechanism into context of a quantitative dose-response model for risk assessment. It is based on the hypothesis that loss of nuclear-mitochondrial intergenomic balance throws the embryo across a threshold for dysmorphogenesis by disrupting a dynamic equilibrium established by tumor suppressor p53.

Approach: Non-linear properties of nuclear-mitochondrial intergenomic signaling will be investigated during chemical teratogenesis in mouse embryos differing by their p53 genotype. Wild-type p53(+/+) and p53(-/-) null mutant embryos will be dosed with 2-chlorodeoxyadenosine (2CdA) on gestational day 8. This research prototype induces specific eye malformations that are predetermined by the embryo's p53 genotype. Dosages in the range of 0.005- to 5.0 mg/kg will be used to go well below the threshold for developmental toxicity (0.5 mg/kg). HPLC-fluorescence and quantitative RT-PCR will measure mitochondrial parameters and a transdominant negative p53 miniprotein targeted to the mitochondrion will be used to genetically alter the biological threshold of embryonic cells.

Expected Results: We expect to provide the first evidence that nuclear-mitochondrial intergenomic balance is an early dosimeter for chemical dysmorphogenesis. Non-linear properties of metabolic control in the embryo can lead to complex dynamic behavior of the mitochondrial genetic system. The proposed research is intended to model this complex behavior in quantitative terms, ultimately linking dose-response relationships into a mechanistic model that can predict when a chemical exposure might cause the embryo to cross the threshold for dysmorphogenesis, leading to structural birth defects or developmental disabilities in the newborn infant.

Improvements in Risk Assessment: An important problem facing risk assessment for environmental contaminants is to incorporate mechanistic information into dose-response assessments in a way that improves the overall quality of low-dose risk prediction in the exposed human population. The data generated here will be amenable to biomathematical modeling and computer simulations to help risk assessors predict when a prenatal environmental exposure might trigger an altered developmental phenotype.

Supplemental Keywords: (do not duplicate terms used in text)
mouse, mitochondrion, mechanisms, low-dose extrapolation, functional assays, bioenergetics